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Efficient solvent-free iron(III) catalyzed oxidation of alcohols by hydrogen peroxide

Sandra E. Martín* and Analía Garrone

INIFQC-Dpto. de Química Orgánica, Fac. de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, 5000-Córdoba, Argentina

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Abstract—Selective oxidation of secondary and benzylic alcohols was efficiently accomplished by H_2O_2 under solvent-free condition catalyzed by $FeBr_3$. Secondary alcohols are selectively oxidized even in the presence of primary ones. This method is high yielding, safe and operationally simple. © 2002 Elsevier Science Ltd. All rights reserved.

The oxidation of alcohols plays an important role in organic synthesis while the development of new oxidative processes continues drawing attention in spite of the availability of numerous oxidizing reagents.¹ Such oxidizing reagents often used in stoichiometric amounts are often hazardous or toxic. Hence, in terms of economical and environmental concern, catalytic oxidation processes with inexpensive and environmental oxidants are extremely valuable. One favorite oxidant to resort to is hydrogen peroxide due to its environmental impact, since water is the only by product of such oxidative reactions.² Although a variety of different catalytic systems for the hydrogen peroxide oxidation of alcohols has been developed,³ there is a growing interest in the search for new efficient metal catalysts for this concern. Many molybdenum- and tungsten-based catalytic systems using hydrogen peroxide have been reported.⁴ Additionally, many examples with manganese catalysts and hydrogen peroxide were described. Manganese-containing polyoxometalate has been used as an effective catalyst for alcohol oxidation.^{3b} Benzylic alcohols could be oxidized by a dinuclear manganese(IV) complex.⁵ The system hydrogen peroxide–manganese(IV) complex transforms secondary alcohols into their corresponding ketones with good yields at room temperature.⁶ Several other systems using aqueous hydrogen peroxide as the oxidant and metal catalysts under phase-transfer catalytic conditions have been reported.⁷ Noyori has described a tungstate-based biphasic system using a phase-transfer catalyst,⁸ a more effective solvent-free version of the process previously

reported by Venturello.⁹ Recently, microwave-assisted oxidation using aqueous hydrogen peroxide and commercially available phase-transfer catalyst was reported.¹⁰ On the other hand, while oxidations by hydrogen peroxide catalyzed by ferrous ions (Fenton's reagent) have been carefully investigated,¹¹ catalyzed oxidations with Fe(III) have received considerably less attention. It has been noticed that besides the normal oxidation of saturated hydrocarbons in Gif-type oxidation reactions, alcohols could be transformed into their corresponding ketones with good yields using Fe(III) catalysts and *t*-butyl hydroperoxide.¹² Otherwise, Fe(III) nitrate catalyzed the oxidation of ethanol with hydrogen peroxide in a fed-batch reactor.¹³ On the other hand, the reaction of Fe(III) porphyrin and non-porphyrin complexes with H_2O_2 has been extensively studied, with the aim of elucidating the mechanisms of the O–O activation and oxygen atom transfer reactions.¹⁴

Herein, we reported a very efficient and selective oxidation of non-activated secondary alcohols with H_2O_2 catalyzed by $FeBr_3$, developed under mild conditions and affording products in high yields. The reaction can take place under organic-aqueous biphasic conditions or under organic-solvent-free conditions. The major advantage of this method apart from the solvent-free conditions is that it does not require a metal complex or phase-transfer condition.

The oxidation of alcohols was carried out at room temperature in the presence of catalytic amounts of $FeBr_3$ and using H_2O_2 as oxidant (Eq. (1)) in an aqueous/organic biphasic system or solvent-free condi-

* Corresponding author. Tel.: +54-351-433-4173; fax: +54-351-433-3030; e-mail: martins@dco.fcq.unc.edu.ar

tions. Menthol was selected as a model substrate for the optimization process. A typical experimental procedure was quite simple: To the FeBr_3 (0.2 mmol) in 5 mL of the organic solvent (or without solvent) was added the substrate (1 mmol) and then hydrogen peroxide (5 mmol, 30%) was slowly incorporated. The reaction mixture was stirred at room temperature for 24 hours. Yields were determined by gas chromatographic assays using an internal standard. Results are shown in Table 1.

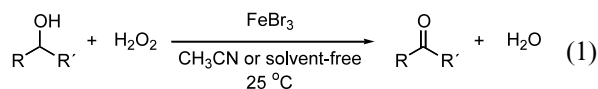


Table 1. Oxidation reaction of menthol to menthone with hydrogen peroxide as oxidant^a

Entry	Catalyst	Solvent	Yields ^b (%)
1	FeBr_3	CH_3CN	92
2	FeBr_3	AcOEt	89
3	FeBr_3	–	18
4	FeBr_3^c	CH_3CN	72
5	FeCl_3	CH_3CN	26
6	$[(\text{FeBr}_3)_2(\text{DMSO})_3]$	CH_3CN	74
7	KBr^d	CH_3CN	N.R. ^e

^a Reactions were carried out with 1 mmol of the alcohol at room temperature, with 0.2 mmol of FeBr_3 and 5 mmol of 30% aqueous H_2O_2 for 24 h.

^b Determined by GC.

^c Reaction carried out with 0.15 mmol of FeBr_3 .

^d Reaction carried out with only 0.75 mmol of KBr .

^e N.R.: reaction did not occur.

The large excess amount of hydrogen peroxide required is a result of its decomposition in the presence of the FeBr_3 catalyst. The oxygen released in the decomposition reaction plays no role in the oxidation of alcohols. No oxidation takes place by performing a reaction under similar conditions but using oxygen as oxidant. The first variable examined was the solvent. Previous work by this group on the aerobic oxidation of alcohols by Fe(III) ¹⁵ suggested that CH_3CN is likely to be the solvent of choice for Fe(III) transformations. The system consisting of FeBr_3 in acetonitrile with H_2O_2 led to the efficient oxidation of menthol (92%) within 24 hours (entry 1, Table 1). Yet, other solvents were examined. The use of AcOEt (entry 2, Table 1) as solvent yielded similar results as acetonitrile. Other reaction solvents such as CH_2Cl_2 , MeOH or benzene were not useful for this reaction, moreover, without organic solvent the oxidation of menthol was not successful (entry 3, Table 1).

In order to improve the efficiency of the catalytic system we examined different ratios among the substrate, the metallic salt and the H_2O_2 . The best results were found when the ratio substrate: H_2O_2 : FeBr_3 was 1:5:0.20. The use of lower amounts of catalyst led to lower yields (entry 4, Table 1). Control experiments revealed that in the absence of FeBr_3 , only less than 1% of the oxidized product was detected. Attempted oxida-

tion with only FeBr_3 without any oxidant under the same conditions resulted in no reaction. No improved rates could be observed at higher temperatures. The oxidation reaction was found to be dependent on the Fe(III) salt. For instance, the use of FeCl_3 as catalyst revealed large differences in the conversion rate of menthol into menthone (entry 5, Table 1). Oxidation can also be carried out with the complex $[(\text{FeBr}_3)_2(\text{DMSO})_3]$ (entry 6, Table 1). This complex was synthesized as previously reported.¹⁶ The main advantage of the use of this coordination compound is its high stability unlike anhydrous FeBr_3 , which facilitates storage and handling and reacts similarly to FeBr_3 .¹⁷ The reaction did not occur varying from FeBr_3 to KBr (entry 7, Table 1).



































Having established what appeared to be the optimal conditions, we switched our attention to the substrate. A series of alcohols was then reacted against this remarkably simple procedure and the results are present in Table 2. The catalytic oxidation was carried out at room temperature using FeBr_3 and H_2O_2 with acetonitrile as solvent (System A). Although the oxidation of menthol carried out under the same conditions without organic solvent (entry 2, Table 2) was not successful, interesting results were obtained for the catalytic oxidation with all other alcohols in solvent-free conditions (System B). Aqueous hydrogen peroxide in the presence of catalytic amount of FeBr_3 without solvent results in slightly improved rates in the oxidation. This is an important feature of this catalytic oxidation. Actually, we have found that there is no need for phase-transfer reagent, as in the solvent-free oxidations previously described.^{8,10}

As shown, the system $\text{FeBr}_3/\text{H}_2\text{O}_2$ was found to be selective, both secondary and benzylic alcohols were oxidized in good yields. All the reactions occurred with complete selectivity for ketones or aldehydes and no other products were detected in the reaction mixture. The products could be readily isolated. Yields were confirmed either by gas chromatography using an internal standard or when products were isolated by column chromatography with an appropriate combination of ethyl acetate/hexanes.

The reaction works well with sterically hindered alcohols such as menthol (entry 1, Table 2) or 2-adamantanol (entry 3, Table 2). The 2-adamantanol required longer reaction times for the same conversion rate than did other cyclic alcohols. The oxidation reactions, therefore, appear not to be quite sensitive to steric factors near the alcohol functional group. With these crystalline alcohols it is necessary to run the reaction with organic solvent in order to achieve good yields (entries 1–4, Table 2). The same pattern was observed in the solvent-free system described by Noyori.⁸

Many other secondary cyclic alcohols were efficiently oxidized in both systems (entries 5–8, Table 2). The catalytic oxidation can also be successfully performed with aliphatic secondary alcohols (entries 9–12, Table 2). For instance, the oxidation of 2-butanol selectively

Table 2. Oxidation of alcohols with hydrogen peroxide catalyzed by Fe(III) in acetonitrile (System A) or without solvent (System B)^a

Entry	Substrate	System	Product	Yield ^b (Isolated Yield) (%)
1		A		92 (88)
2		B		18
3 ^c		A		91 (87)
4 ^c		B		25
5		A		83
6		B		90 (85)
7		A		89
8		B		92 (87)
9		A		94
10		B		95 (91)
11		A		86
12		B		90 (86)
13		A		N.R. ^d
14		A		82
15		B		89 (84)
16		A		70
17		B		91 (86)

^a System A: Reaction carried out with 1 mmol of the substrate in 5 mL of CH₃CN in an open system at room temperature, for 24 hours, in a molar ratio substrate:H₂O₂:FeBr₃ 1:5:0.20 mmol. System B: Reactions were carried out under the same conditions as in System A, without organic solvent.

^b Determined by GC.

^c Reaction time: 36 hours.

^d N. R.: Reaction did not occur.

gave 2-butanone in 95% yield (entry 10, Table 2). It should be noticed that simple primary alcohols were not oxidized to the corresponding carbonyl product and the starting alcohol was recovered (entry 13, Table 2). Besides, secondary aliphatic alcohols were selectively oxidized even in the presence of primary ones (entries 14–15, Table 2). Trost^{4b} found the same selectivity in a molybdenum catalyzed alcohol oxidation by hydrogen peroxide. Benzylic alcohols behave quite differently from aliphatic ones and the oxidation of benzyl alcohol produced benzaldehyde in good yield with no over oxidation (entries 16–17, Table 2). This behavior is simple to explain because of the reactivity of benzylic alcohols. Surprisingly, benzyl alcohol is converted to benzaldehyde more efficiently in the solvent-free system than in the other one. Finally, the oxidation of alcohols to the corresponding carbonyl compounds is well known to take place by high-valent metal complexes.^{1a,12} Therefore, the alcohol oxidation with the system FeBr₃/H₂O₂ could be achieved via high-valent iron species.

In conclusion, organic-solvent-free oxidation of alcohols using aqueous hydrogen peroxide, an ideal oxidant, in the presence of catalytic amounts of FeBr₃

provides a general, safe, and simple method for secondary and benzylic alcohols oxidation. Secondary alcohols are selectively oxidized even in the presence of primary ones. The reaction under very mild conditions is high yielding and easy to implement. An important advantage of this method aside from the solvent-free conditions is that it does not require a phase-transfer catalyst.

General Procedure. Oxidation Reactions with H₂O₂ catalyzed by FeBr₃. A typical experiment was carried out in an open reaction tube fitted with a condenser. To the catalyst FeBr₃ (0.20 mmol) in 5 mL of CH₃CN (or solvent-free) menthol was added (1 mmol). Then hydrogen peroxide (5 mmol, 30%) was slowly incorporated. The reaction mixture was stirred at room temperature for 24 h. GC was used to follow the reaction. When the reaction was complete, CH₂Cl₂ was added and both phases were separated. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with water, dried over MgSO₄, and the solvent was removed in vacuo. The residue was chromatographed on a silica gel (70–270 mesh ASTM) column, and eluted with ethyl acetate/hexanes using various ratios. All products identified were found to be identical to authentic samples.

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